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最終頁に続く

(54)【発明の名称】　ハイドロキシアパタイト球状粒子とその製造方法、及びこれを用いた生体材料

(57)【要約】
【課題】ヒトや動物の歯牙根管内の充填材、抜歯眼窩への充填材、顎堤再建材などの生体材料として有用なハイドロキシアパタイト球状粒子、及びこれを用いた生体材料を提供する。
【解決手段】平均粒径が０．５～２００μｍであり、かつ前記球状粒子１ｇを水２５ｇに撹拌したときのｐＨ値が８～１２であるハイドロキシアパタイト球状粒子、および水酸化カルシウムを１～２０重量％含む懸濁液にｐＨ値が９～１２となるようにリン酸水溶液を添加し、前記懸濁液の温度が５０℃を越えないようにコントロールしながら非晶質リン酸カルシウムを合成し、次いで、得られた非晶質リン酸カルシウムスラリーを造粒乾燥し、一旦平均粒径が０．５～２００μｍの非晶質リン酸カルシウム球状粒子を得た後、前記球状粒子を８００～１３００℃で焼成することにより骨形成能力に優れたハイドロキシアパタイト粒子を製造し、そのハイドロキシアパタイト球状粒子を生体材料として利用する。

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【特許請求の範囲】

【請求項１】骨形成能力に優れたハイドロキシアパタイト球状粒子であって、平均粒径が０．５～２００μｍであり、かつ前記球状粒子１ｇを水２５ｇに撹拌したときのｐＨ値が８～１２であることを特徴とするハイドロキシアパタイト球状粒子。

【請求項２】Ｃａ／Ｐモル比が１．６０～２．００であることを特徴とする請求項１に記載のハイドロキシアパタイト球状粒子。

【請求項３】水酸化カルシウムを１～２０重量％含む懸濁液にｐＨ値が９～１２となるようにリン酸水溶液を添加し、前記懸濁液の温度が５０℃を越えないようにコントロールしながら非晶質リン酸カルシウムを合成し、次いで、得られた非晶質リン酸カルシウムスラリーを造粒乾燥し、一旦平均粒径が０．５～２００μｍの非晶質リン酸カルシウム球状粒子を得た後、前記球状粒子を８００～１３００℃で焼成することを特徴とするハイドロキシアパタイト球状粒子の製造方法。

【請求項４】前記非晶質リン酸カルシウムスラリーの合成時に、水酸化カルシウム懸濁液に中性または弱アルカリ性の水溶性高分子分散剤を添加して混合溶液とした後、その混合溶液を撹拌しながらリン酸水溶液を滴下してｐＨを９～１２に調整する請求項３に記載の製造方法。

【請求項５】請求項１または２に記載のハイドロキシアパタイト球状粒子を含むことを特徴とする生体材料。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、ヒトや動物の歯牙根管内の充填、抜歯窩への充填および顎堤再建などに使用可能なハイドロキシアパタイト球状粒子とその製造方法及びこれを用いた生体材料に関する。

【０００２】

【従来の技術】近年、生体材料、とくに骨代替材料に関する報告が認められる。外科あるいは整形外科の分野において、骨折や骨腫瘍に対する手術により、骨欠損あるいは空隙が生じる。また、歯科の分野においても、歯槽膿漏による顎骨の消耗が起こる。現在、これらの問題に対して、患者の腸骨等より骨片を採取し、骨欠損部に充填し当該組織の回復治癒を早めるという方法が取られている。しかしながら、この術式は患者の正常部位から骨移植片を採取するため、肉体的、精神的負担が大きいことが指摘されている。また、患部が広範囲に及ぶ場合には、移植骨片の採取が量的に困難な症例にも遭遇する。そのため、骨代替材料の利用が求められているが、移植部位における拒絶ならびに排出反応がみられ、予後は必ずしも良好とは言えない。したがって、骨代替材料の臨床応用は未だ実験段階を脱していないのが実情である。

【０００３】このような背景から、良好な生体適合性を示し、かつ、修復が望まれる骨欠損部位の形態的・機能

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的回復を促進する人工の骨代替材料の開発が期待されている。そこで、特開昭５６－５４８４１号公報では骨欠損部及び空隙部充填材、並びに該充填材を用いた動物の骨の治療方法が記載されている。ここで、$Ca_m(PO_4)_n \cdot OH$（１．３３≦ｍ／ｎ≦１．９５）を有する結晶粒径が５０Å～１０μｍのアパタイト型結晶構造リン酸カルシウム化合物の粉粒体を含有せしめ、前記充填材を流動状態又は過疎状態とする骨組織と一体化させるための充填材が開示されているが骨形成が遅いという欠点があった。

【０００４】

【発明が解決しようとする課題】本発明は、ヒトや動物の歯牙根管内の充填材、抜歯窩への充填材、顎堤再建材等として好適に使用できるハイドロキシアパタイト球状粒子を提供することを目的とする。

【０００５】

【課題を解決するための手段】本発明者等は、上記の問題を解決すべく、歯牙根管内の充填材、抜歯窩への充填材、顎堤再建材等として有用なハイドロキシアパタイト粒子について種々検討した結果、水酸化カルシウムを１～２０重量％含む懸濁液にリン酸水溶液を添加し、ｐＨを９～１２に調整して非晶質リン酸カルシウムを合成するに際して、合成時の前記懸濁液の温度が５０℃を越えないようにコントロールすることによって得られた非晶質リン酸カルシウムスラリーを造粒乾燥し、一旦平均粒径が０．５～２００μｍの非晶質リン酸カルシウム球状粒子を得た後、前記球状粒子を８００～１３００℃で焼成することを特徴とするハイドロキシアパタイト粒子であって、かつ前記球状粒子１ｇを水２５ｇに撹拌したときのｐＨ値が８～１２であることを特徴とするハイドロキシアパタイト球状粒子が、生体に対して安全で、かつ、骨形成能がきわめて早いという特異な作用効果を有することを見いだし、本発明を完成させるに至った。

即ち、本発明は以下の発明を包含する。

（１）　骨形成能力に優れたハイドロキシアパタイト球状粒子であって、平均粒径が０．５～２００μｍであり、かつ前記球状粒子１ｇを水２５ｇに撹拌したときのｐＨ値が８～１２であることを特徴とするハイドロキシアパタイト球状粒子。

（２）　Ｃａ／Ｐモル比が１．６０～２．００であることを特徴とする（１）項に記載のハイドロキシアパタイト球状粒子。

（３）　水酸化カルシウムを１～２０重量％含む懸濁液にｐＨ値が９～１２となるようにリン酸水溶液を添加し、前記懸濁液の温度が５０℃を越えないようにコントロールしながら非晶質リン酸カルシウムを合成し、次いで、得られた非晶質リン酸カルシウムスラリーを造粒乾燥し、一旦平均粒径が０．５～２００μｍの非晶質リン酸カルシウム球状粒子を得た後、前記球状粒子を８００～１３００℃で焼成することを特徴とするハイドロキシ

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アパタイト球状粒子の製造方法。

（４）　前記非晶質リン酸カルシウムスラリーの合成時に、水酸化カルシウム懸濁液に中性または弱アルカリ性の水溶性高分子分散剤を添加して混合溶液とした後、その混合溶液を撹拌しながらリン酸水溶液を滴下してｐＨを９～１２に調整する（３）項に記載の方法。

（５）　上記（１）項または（２）項に記載のハイドロキシアパタイト球状粒子を含むことを特徴とする生体材料。

【０００６】

【発明の実施の形態】本発明でいうハイドロキシアパタイト（Hydroxyapatite：以下ＨＡｐと略すことがある）とは、式$Ca_{10}(PO_4)_6(OH)_2$で表されるリン酸カルシウム系化合物を代表とするものであって、その結晶構造中のＣａがたとえばチタン、亜鉛、セリウム、バリウム、ストロンチウム、マグネシウム、ナトリウム、カリウム、鉄またはアルミニウムに、PO_4がたとえばVO_4、SiO_4またはCO_3に、ＯＨがＦ、Ｃｌ、Ｂｒ、Ｉ、Ｎ、ＯまたはCO_3に置換されていてもかまわない。また、酸化チタン、アルミナ、ジルコニアのような金属酸化物を１種もしくは２種以上複合していてもよく、金属酸化物の種類については特に限定されない。さらに、天然物、セラミックス、無機物、有機物、カーボン等で生体親和性があるものが複合されていてもかまわない。

【０００７】前記のように、本発明のＨＡｐ球状粒子は、平均粒径が０．５～２００μｍであり、かつ前記球状粒子１ｇを水２５ｇに撹拌したときのｐＨ値が８～１２であることを特徴とするものであり、かかるハイドロキシアパタイト球状粒子を用いて、動物実験を行うと、理由は定かではないが骨形成が非常に早く、これに比較して上記ｐＨ値が８未満のＨＡｐ粒子を用いるとき、骨形成が遅いことがわかった。

【０００８】本発明のＨＡｐ球状粒子は、水酸化カルシウムを１～２０重量％含む懸濁液にリン酸水溶液を添加してｐＨを９～１２に調整することにより合成される非晶質リン酸カルシウムスラリーを造粒乾燥し、一旦平均粒径が０．５～２００μｍの非晶質リン酸カルシウム球状粒子を得た後、前記球状粒子を８００～１３００℃で焼成することにより得られるものである。

【０００９】造粒乾燥法を採用することにより、平均粒径０．５～２００μｍのＨＡｐ球状粒子が得られやすく、この方法では平均粒径２００μｍ以上のＨＡｐ球状粒子は得られにくく、また０．５μｍ以下の球状粒子もその回収率がきわめて低い。上記の製造方法において、非晶質リン酸カルシウムの合成時のｐＨが９未満になると、得られたＨＡｐ球状粒子は、その１ｇを水２５ｇに撹拌したときのｐＨ値が８未満となり、本発明で目的とする性状のものが得られない。また、合成時の温度は、５０℃を越えないように調整されるが、この温度を越えると第２リン酸カルシウムが生成する場合があり、このものは数十μｍの板状粒子であるために、均一な球状粒子にはなりにくい。上記温度が５０℃を越えないようにするためには、水酸化カルシウムを含む懸濁液等を、例えば、２０℃以下に予め冷却してから合成に供してもよいし、冷却設備を備えた反応器を使用してコントロールしてもよい。

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【００１０】本発明のＨＡｐ球状粒子が大きな比表面積を獲得するように、その製造工程においてスラリー中含まれる非晶質リン酸カルシウム（以下、ＡＣＰ粒子と称すことがある）の一次粒子の平均粒子径は０．１μｍ未満であるのが望ましい。なお、本明細書における球状粒子の粒径は、レーザー回折法により測定したものである。

【００１１】また、非晶質リン酸カルシウムスラリーの合成時に、水酸化カルシウム懸濁液に、撹拌下、中性または弱アルカリ性の水溶性高分子分散剤を添加して混合溶液とした後、その混合溶液を撹拌しながらリン酸水溶液を滴下してｐＨを９～１２に調整してもよい。この場合にも、懸濁液の温度が５０℃を超えないようにコントロールすることが必要である。

【００１２】前記水溶性高分子分散剤は、スラリー中に含まれる粒径約０．１μｍ未満の一次ＡＣＰ粒子の凝集を回避するために添加されるものであり、ハイドロキシアパタイトの合成を阻害せずに、この目的を達するものを任意に選択し得る。その好ましい具体例としては、弱アルカリ性のトリアクリル酸アンモニウム塩，ポリアクリル酸塩、ニトロフミン酸塩、リグニンスルホン酸塩またはスチレン－無水マレイン酸共重合体等あげられる。水溶性高分子分散剤添加量は水酸化カルシウム懸濁液量に対して０．１～１０重量％、好ましくは０．１～３重量％である。

【００１３】本発明のＨＡｐ球状粒子は、ヒトや動物の歯牙根管内の充填材、抜歯窩への充填材、顎堤再建材等として使用することにより、きわめて早い骨形成作用を有する。したがって、生体材料、とくに骨代替材料として有利に使用できる。

【００１４】

【実施例】以下、実施例、比較例および試験例を挙げて本発明をさらに詳細に説明する。ただし、本発明は以下の実施例に限定されるものではない。

実施例１

本発明のＨＡｐ球状粒子を次にようにして製造した。水酸化カルシウム１０％懸濁液１０リットルを、撹拌下、約１０℃に冷却した後、水溶性高分子分散剤として弱アルカリ性のトリアクリル酸アンモニウム塩を５０ｇ（０．５重量％）添加して、混合溶液を得た。得られた混合溶液を撹拌しながら、８５％リン酸溶液を水で１０倍に希釈したリン酸水溶液を滴下し、ｐＨを１０．５に調整することにより、ＡＣＰスラリーを合成した。この

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合成反応中、懸濁液の温度は最高３７℃であって、５０℃を越えることはなかった。このようにして、粒径約０．１μm未満の一次ＡＣＰ粒子を含むスラリーを得た。

【００１５】上記スラリーを用いて、噴霧乾燥造粒法により、ＨＡｐ球状粒子を製造した。このときに用いた噴霧乾燥造粒装置の概略図を図１に示す。この図１において、９はエアフィルター、１０は電気ヒータであり、エアフィルター９を通り電気ヒータ１０によって加温された熱空気は、熱ガス室１１からスプレードライヤー５内に入り、スプレードライヤー５のアトマイザー６により噴霧されるスラリー３を乾燥造粒しつつ、排出孔１２からサイクロン８に向けて流出するようになっている。

【００１６】得られた一次ＡＣＰ粒子１を含むスラリー３を、定量ポンプ４によりスプレードライヤー（大川原化工機械社製ＯＤＢ－２５Ｇ）５のアトマイザー６に供給した。そのアトマイザー６を高速回転させて、スプレードライヤー５内の乾燥用の熱空気流中に上記混合物スラリー３を噴霧し、噴霧乾燥造粒法により造粒した。この造粒によって、ＡＣＰ多孔質な球状粒子７を得た。

【００１７】得られた上記ＡＣＰ多孔質粒子７は、サイクロン８によって採取した。このとき、サイクロン８により採取しきれない超微粉体はバグフィルター（図示せず）により別に採取した。なお、上記造粒における操作条件は次の通りであった。定量ポンプ４による混合物スラリー３の供給量は１～３kg/hであり、エアフィルター９を介して電気ヒーター１０によって加温された熱空気の温度は、熱ガス室１１の入口温度が１５０～３５０℃に、サイクロン８に繋がる排出孔１２における出口温度が８０℃を常に超えるように制御し、また、アトマイザー６の回転数は１００００～３００００rpmの範囲内に設定した。

【００１８】このようにして得られたＡＣＰ多孔質粒子７は、噴霧乾燥造粒法を用いたことにより多孔質な球状となり、平均粒子径は３５μmであった。上記、ＡＣＰ粒子をアルミナ坩堝に入れ、１２００℃で１時間焼成し，ＨＡｐ球状粒子を得た。このＨＡｐ球状粒子を１ｇとり、イオン交換水２５ｇ中に入れ、スターラーで１０分間撹拌した後、ろ過し、ろ液のｐＨを測定したところ、９．６であった。

【００１９】比較例１

水酸化カルシウム１０％懸濁液を、撹拌下、約１０℃に冷却した後、水溶性高分子分散剤として弱アルカリ性のトリアクリル酸アンモニウム塩を０．５重量％添加して、混合溶液を得た。得られた混合溶液を撹拌しながら、８５％リン酸溶液を水で１０倍に希釈したリン酸水溶液を滴下し、ｐＨを８．５に調整することにより、ＡＣＰスラリーを合成した。この合成反応中、懸濁液の温度は最高３７℃であって、５０℃を越えることはなかった。このようにして、粒径約０．１μm未満の一次ＡＣＰ粒子を含むスラリーを得た。これを、実施例１と同様な条件下において、乾燥造粒、焼成を行って得られたＨＡｐ粒子を１ｇとり、イオン交換水２５ｇ中に入れ、スターラーで１０分間撹拌した後、ろ過し、ろ液のｐＨを測定したところ、７．５であった。

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【００２０】試験例１

（動物実験）

材料

実施例１において作製したＨＡｐ球状粒子と比較例１にて作製したＨＡｐ粒子を用いた。また、Sprague-Dawley系ラット（７週齢、雄）を実験動物として使用した。

【００２１】実験方法

歯科用ラウンドバーを用いて、全身麻酔を施したラットの頭蓋骨に直径約２．５mmの欠損部を作製した。この欠損部に肉眼的に十分な量のＨＡｐをそれぞれ充填した。充填後、２および４週間後に頭蓋骨を採取し、１０％中性ホルマリン溶液で固定した。病理組織学的観察に際し、頭蓋骨を１０％ＥＤＴＡ溶液で脱灰した後、ＨＡｐ充填部を切り出し、アルコール脱水およびキシレン透徹を行い、パラフィンに包埋した。その後、約４μmの組織標本を作製し、これにヘマトキシリン・エオジン染色を施し、光学顕微鏡による観察、撮影を行った。

【００２２】成績

実施例１のＨＡｐ球状粒子を補填し、２週間後の顕微鏡写真を図２に、比較例１のＨＡｐを充填し、2週間後の顕微鏡写真を図３に示す。これらの顕微鏡写真において、Ｂは頭蓋骨（既存の骨）、矢印は欠損部の断端を示す。両ＨＡｐ粒子充填例はともに骨伝導所見が観察されるが、実施例１のＨＡｐ充填剤では欠損部内に新生骨組織がみられる。このことから、実施例１のＨＡｐ粒子は比較例１のＨＡｐ粒子に比べ、骨組織に対してより適切な環境を提供していることがうかがわれる。

【００２３】実施例１のＨＡｐ球状粒子を補填し、４週間後の顕微鏡写真を図４に、比較例１のＨＡｐを補填し、４週間後の顕微鏡写真を図５に示す。これらの顕微鏡写真において、Ｂは頭蓋骨（既存の骨）、ｂは新生骨、ｃは結合組織、ＨはＨＡｐ粒子、矢印は欠損部の断端を示す。図４が示すように、実施例１のＨＡｐ粒子充填例では新生骨内に多数のＨＡｐ粒子が取り込まれている。これに対し、比較例１のＨＡｐ粒子充填例では、骨の新生程度が悪く、ＨＡｐ粒子が結合組織に囲まれたままである。また、実施例１のＨＡｐ粒子充填例の顕微鏡写真（図４）では、筋状の傷が多数認められる。これは、脱灰処理を施しているにもかかわらず新生した骨組織があまりにも硬いため、病理組織標本作製時にできたものであり、新生骨が非常に強いことを示唆している。

【００２４】

【発明の効果】本発明のハイドロキシアパタイト粒子は、骨形成能力に優れており、骨補填材、歯牙根管内の充填材、抜歯窩への充填材および顎堤再建材として好適

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に使用することができる。

【図面の簡単な説明】

【図１】本発明の非晶質リン酸カルシウム粒子の製造に用いる造粒乾燥装置を示す図である。

【図２】実施例１で得られたＨＡｐ球状粒子をラット頭蓋骨の欠損部に補填し、２週間経過後の顕微鏡写真を示す。

【図３】比較例１で得られたＨＡｐ粒子をラット頭蓋骨の欠損部に補填し、２週間経過後の顕微鏡写真を示す。

【図４】実施例１で得られたＨＡｐ球状粒子をラット頭蓋骨の欠損部に補填し、４週間経過後の顕微鏡写真を示す。

【図５】比較例１で得られたＨＡｐ粒子をラット頭蓋骨の欠損部に補填し、４週間経過後の顕微鏡写真を示す。

【符号の説明】

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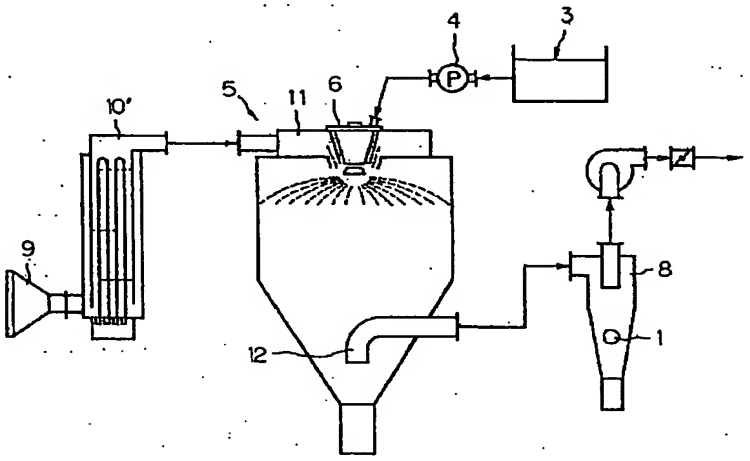
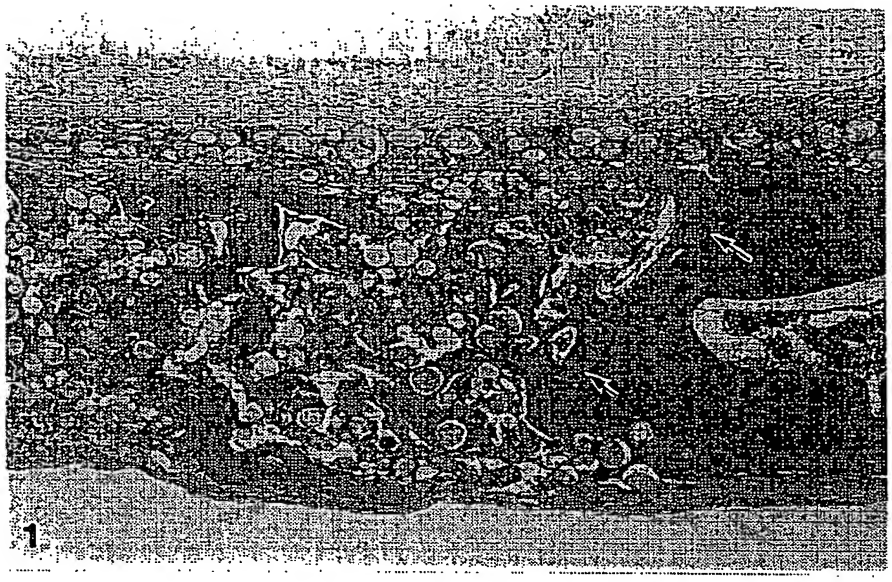
１：一次ＡＣＰ粒子
３：一次ＡＣＰ粒子を含むスラリー
４：定量ポンプ
５：スプレードライヤー
６：アトマイザー
７：ＡＣＰ多孔質粒子
８：サイクロン
９：エアフィルター
１０：電気ヒータ
１１：熱ガス室
１２：排出孔
Ｂ：頭蓋骨（もともとあった骨）
ｂ：新生骨（新しくできた骨）
ｃ：結合組織
Ｈ：アパタイト粒子

【図１】



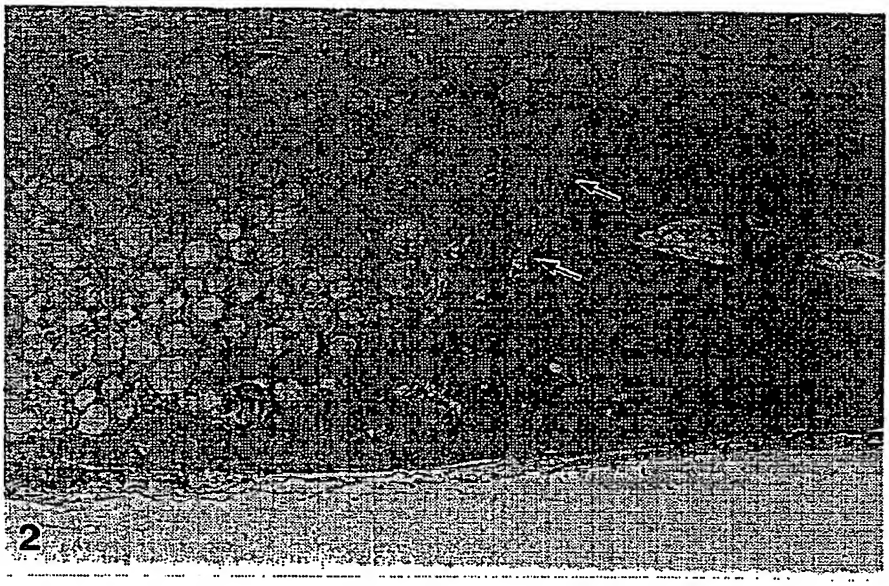
【図２】

図面代用写真



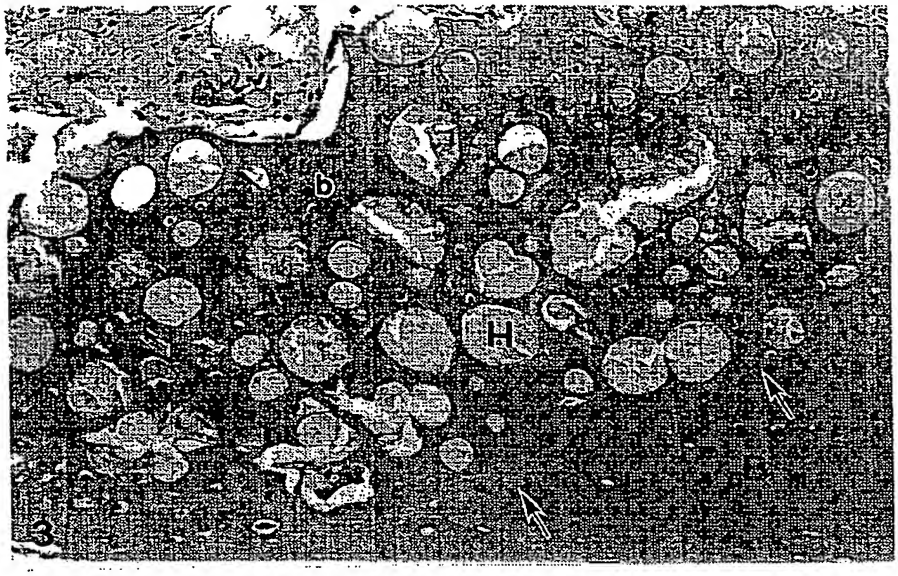
【図３】

図面代用写真



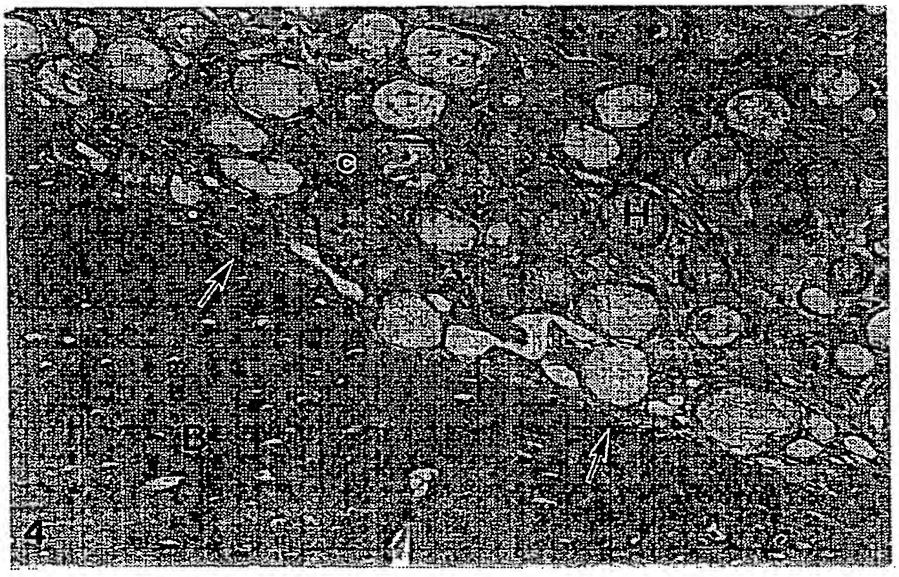
【図４】

図面代用写真



【図５】

図面代用写真



フロントページの続き

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CA07 CA08

Japanese Patent Application Laid-Open No. 2000-42096

(54) [Title of Invention] HYDROXYAPATITE SPHERICAL PARTICLE, METHOD OF PREPARING THE SAME, AND BIOMATERIAL USING THE SAME

(57) [Abstract]

[Problem] To provide a hydroxyapatite spherical particle which can be preferably used for a filling material within tooth root canal, a filling material of tooth extraction cavity, a material for reconstructing alveolar ridge and the like of human being and animals, and to provide a biomaterial using the same.

[Means for Solving Problem] A hydroxyapatite spherical particle whose bone formation capability is excellent and which is characterized in that the average particle diameter is in the range from 0.5 to 200 μm, and the pH value at the time when 1 g of the spherical particle is agitated in 25 g of water is in the range from 8 to 12, is prepared by a method characterized in that when amorphous calcium phosphate is synthesized by adding phosphoric acid aqueous solution in a suspension containing 1-20 % by weight of calcium hydroxide and adjusting pH in the range from pH9 to pH12, an amorphous calcium phosphate slurry is synthesized while controlling the temperature of the suspension not to exceed 50°C, subsequently, the obtained amorphous calcium phosphate slurry is granulized and dried, and the spherical particle is burned at a temperature in the range from 800 to 1300°C after an amorphous calcium phosphate spherical particle having the average particle diameter in the range from 0.5 to 200 μm gas been obtained. The hydroxyapatite spherical particle is used as a biomaterial.

[Scope of Claims]

[Claim 1] A hydroxyapatite spherical particle whose bone formation capability is

excellent and characterized in that the average particle diameter is in the range from 0.5 to 200 μm, the pH value at the time when 1 g of the spherical particle was agitated in 25 g of water is in the range from 8 to 12.

[Claim 2] A hydroxyapatite spherical particle according to claim 1 characterized in that Ca/P molar ratio is in the range from 1.60 to 2.00.

[Claim 3] A method of preparing a hydroxyapatite spherical particle characterized in that at the time when amorphous calcium phosphate is synthesized by adding phosphoric acid aqueous solution in a suspension containing 1-20 % by weight of calcium hydroxide and adjusting pH in the range from pH9 to pH12, an amorphous calcium phosphate slurry is synthesized while controlling the temperature of the suspension not to exceed 50°C, and subsequently, the obtained amorphous calcium phosphate slurry is granulized and dried, the spherical particle is burned at a temperature in the range from 800 to 1300°C after an amorphous calcium phosphate spherical particle having the average particle diameter in the range from 0.5 to 200 μm has been obtained.

[Claim 4] The method according to claim 3 wherein at the time when the amorphous calcium phosphate slurry is synthesized, pH is adjusted in the range from pH9 to pH12 by dropping phosphoric acid aqueous solution while agitating the mixture solution after the mixture solution has been made by adding a neutral or weak alkaline aqueous macromolecular dispersing agent to calcium hydroxide suspension,

[Claim 5] A biomaterial characterized in that it contains a hydroxyapatite spherical particle according to claim 1 or 2.

[Detailed Description of the Invention]

[0001]

[Technical Field Pertinent to the Invention] The present invention relates to a hydroxyapatite spherical particle which can be used for filling tooth root canal of human and animals, for filling a tooth extraction cavity, for reconstruction of alveolar ridge or the like, a method of manufacturing thereof and, a biomaterial utilizing it.

[0002]

[Prior Art] In recent years, the reports relating to a biomaterial, particularly, a bone substituting material have been admitted. In the surgical or orthopedically surgical area, a bone defect or space is generated by the surgery for bone fracture and bone tumor. Moreover, also in the field of dentistry, the consumption of jaw due to alveolar pyorrhoea occurs. At present, for the purpose of dealing with these problems, a method in which a bone fragment is collected from iliac bone or the like of the patient, it is filled in the bone defect portion and the recovery and remedy of the relevant tissue is accelerated is taken. However, since in this operation, bone transplant fragment is collected from the normal site of the patent, it is pointed out that the physical and metal stress of the patent is increased. Moreover, in the case where the affected part is wide in its area, it may be also met with the cases in which the collection of the transplant bone fragment is difficult in terms of volume. Therefore, the utilization of bone substituting material has been required; however, the rejection reaction and elimination reaction are seen in the transplant site, and it cannot be necessarily said that the prognosis is excellent. Therefore, the clinical application of the bone substituting materials actually has not yet found its way out of the experimental stage.

[0003] Since there has been the background as described above, it has been expected that an artificial bone substituting material indicating an excellent biocompatibility is developed for promoting the formational/functional recovery at the bone defect where the restoration is desired. Then, in Japanese Patent Application Laid-Open No. 56-54841, a filling material for bone defect part and cavity part and a method of treating a bone of animals using the relevant filling material have been described. Here, although a filling material for integrating it with a bone tissue that makes the filling material in a fluid state or in an undercrowding state by containing a powdered body of a calcium phosphate compound having an apatite type crystal structure whose crystal particle diameter is in the range from 50 Å to 10 μm and having $Ca_m(PO_4)_nOH$ ($1.33 \leq m/n \leq 1.95$) has been

disclosed, there has been a disadvantage that the formation of the relevant bone is delayed.

[0004]

[Problem to be solved by the Invention] An object of the present invention is to provide a hydroxyapatite spherical particle which can be preferably used as a filling material within tooth root canal, a filling material of tooth extraction cavity, a material for reconstructing alveolar ridge and the like of human being and animals.

[0005]

[Means for Solving Problem] The present inventors have studied and considered a variety of hydroxyapatite particles which are useful as a filling material within tooth root canal, a filling material for tooth extraction cavity, a material for reconstructing alveolar ridge and the like in order to solve the problems. As a result, the present inventors have found that a hydroxyapatite particle characterized in that at the time when amorphous calcium phosphate is synthesized by adding phosphoric acid aqueous solution in a suspension containing 1-20% by weight of calcium hydroxide and adjusting pH in the range from pH9 to pH12, an amorphous calcium phosphate slurry obtained by controlling the temperature of the suspension at the time of synthesizing not tot exceed 50°C is granulized and dried, the spherical particle is burned at a temperature in the range from 800 to 1300°C after an amorphous calcium phosphate spherical particle having the average particle diameter in the range from 0.5 to 200 μm has been obtained, and characterized in that the pH value at the time when 1 g of the spherical particle has been agitated in 25 g of water is in the range from 8 to 12 has a peculiar action effect which is safe for a living organism and whose bone formation capability is extremely rapid, and the present inventors have completed the present invention. Specifically, the present invention includes the following inventions.

(1) A hydroxyapatite spherical particle whose bone formation capability is excellent and characterized in that the average particle diameter is in the range from 0.5 to 200 μm, the pH value at the time when 1 g of the spherical particle is agitated in 25 g of water is in the

range from 8 to 12.

(2) A hydroxyapatite spherical particle described in the article (1) characterized in that Ca/P molar ratio is in the range from 1.60 to 2.00.

(3) A method of preparing a hydroxyapatite spherical particle characterized in that when amorphous calcium phosphate is synthesized by adding phosphoric acid aqueous solution in a suspension containing 1-20% by weight of calcium hydroxide and adjusting pH in the range from pH9 to pH12, an amorphous calcium phosphate slurry is synthesized while controlling the temperature of the suspension not to exceed 50°C, and subsequently, the obtained amorphous calcium phosphate slurry is granulized and dried, the spherical particle is burned at a temperature in the range from 800 to 1300°C after an amorphous calcium phosphate spherical particle having the average particle diameter in the range from 0.5 to 200 μm has been obtained.

(4) The method described in the article (3) in which at the time when the amorphous calcium phosphate slurry is synthesized, pH is adjusted in the range from pH9 to pH12 by dropping phosphoric acid aqueous solution while agitating the mixture solution after the mixture solution has been made by adding a neutral or weak alkaline aqueous macromolecular dispersing agent to calcium hydroxide suspension,

(5) A biomaterial characterized in that it contains a hydroxyapatite spherical particle according to the article (1) or (2).

[0006]

[Mode for Carrying Out the Invention] Hydroxyapatite (hereinafter, it may be abbreviated as HAp) is a compound representing calcium phosphate based compound which is represented by the formula of $Ca_{10}(PO_4)_6(OH)_2$, Ca contained in the crystal structure may be substituted by titanium, zinc, cerium, barium, strontium, magnesium, sodium, potassium, iron or aluminum, PO_4 may be substituted, for example, by VO_4, SiO_4, or CO_3, and OH may be substituted by F, Cl, Br, I, N, O, or CO_3. Moreover, one type or two types or more of metal oxide such as titanium oxide, alumina, zirconia and the like

may be complexed, and the kinds of metal oxide are not particularly limited. Furthermore, a matter or compound such as a natural matter, ceramics, an inorganic, an organic, carbon and the like which has biocompatibility may be complexed.

[0007] As described above, a HAp spherical particle of the present invention is characterized in that its average particle diameter is in the range from 0.5 to 200 μm, and the pH value at the time when 1 g of the spherical particle is agitated in 25 g of water is in the range form 8 to 12, it is found that when the animal test is performed by utilizing such a hydroxyapatite spherical particle, although the reason is uncertain, the bone formation is extremely rapid, and in comparison, when a HAp particle having the pH value less than 8 is used, the bone formation is delayed.

[0008] A HAp particle of the present invention is obtained by granulizing and drying an amorphous calcium phosphate slurry synthesized by adjusting the pH in the range from pH9 to pH12 by adding phosphoric acid aqueous solution to a suspension containing 1-20% by weight of calcium hydroxide, and then, by burning the spherical particle at a temperature in the range from 800 to 1300°C after obtaining an amorphous calcium phosphate spherical particle whose average particle diameter is in the range from 0.5 to 200 μm,.

[0009] A HAP spherical particle having the average particle diameter in the range from 0.5 to 200 μm is easily obtained by employing a method of granulizing and drying. In this method, a HAp spherical particle having the average particle diameter of 200 μm or more is not easily obtained, and the collected ratio of the spherical particle having the average particle diameter of 0.5 μm or less is also extremely low. In the preparation method, in the case where the pH value at the time when an amorphous calcium phosphate is synthesized is 9 or less, as for the obtained HAp spherical particle, the pH value at the time when 1 g of it was agitated in 25 g of water is 8 or less, a matter having the nature that the present invention aimed at is not obtained. Moreover, the temperature at the time of synthesizing it is adjusted to exceed 50°C; however, in the case where the

temperature exceeds the temperature, dibasic calcium phosphate may be generated; therefore, since this is a particle in a plate shape having the size of several dozens of μm, it becomes hardly a uniform spherical particle. In order to keep the temperature 50°C or lower, a suspension containing calcium hydroxide and the like may be first preliminarily cooled to a temperature of 20°C or less, and then, subjected to the synthesizing process, or it may be controlled by utilizing a reactor which is equipped with a cooling facility.

[0010] It is desirable that in the preparation process, the average particle diameter of the primary particle of the an amorphous calcium phosphate (hereinafter, it may be referred to as ACP particle) contained in a slurry is less than 0.1 μm so that a HAp spherical particle of the present invention acquires a large specific surface area. It should be noted that the particle diameters of spherical particles in the present specification are measured by a laser diffraction method.

[0011] Moreover, at the time when an amorphous calcium phosphate slurry is synthesized, while agitating it in a suspension containing calcium hydroxide, after the mixture solution is made by adding a neutral or weak alkaline aqueous macromolecular dispersing agent to the suspension containing calcium hydroxide, the pH value may be adjusted by dropping the phosphoric acid aqueous solution while agitating the mixture solution. Also in this case, it is necessary to control the temperature of the suspension not to exceed 50°C.

[0012] The aqueous macromolecular dispersion agent is added for the purpose of avoiding the aggregation of the primary ACP particle whose particle diameter is less than about 0.1 μm contained in a slurry, and the dispersing agent which achieves the object without inhibiting the synthesis of hydroxyapatite can be optically selected. As its preferable concrete example, weak alkaline ammonium triacrylate, polyacrylate, nitrofumicate, ligninsulfonate, styrene-maleic anhydride copolymer or the like is listed. As for an amount of addition of an aqueous macromolecular dispersing agent, it is in the range from 0.1 to 10% by weight and it is preferable that it is in the range from 0.1 to 3%

by weight.

[0013] A HAp spherical particle of the present invention has an extremely rapid bone formation action as being utilized as a filling material within a tooth root canal, a filling material for tooth extraction cavity, a material for reconstructing alveolar ridge and the like of human being or animal. Therefore, it can be advantageously used as a biomaterial, particularly as a bone substituting material.

[0014]

[Examples] Hereinafter, the present invention will be further explained in detail by describing Examples, Comparative Examples and the Test Examples. However, the present invention is not limited by the following Examples.

Example 1

A HAp spherical particle of the present invention was manufactured as follows: after 10 L of 10% calcium hydroxide suspension was cooled to about 10°C while agitating it, 50 g (0.5% by weight) of weak alkaline ammonium triacrylate as an aqueous dispersing agent was added, and the mixture solution was obtained. While the mixture solution was agitated, phosphoric acid aqueous solution in which 85% phosphoric acid aqueous solution had been diluted with water into 10-fold was dropped, and then, an ACP slurry was synthesized by adjusting pH into 10.5. In the synthesis reaction, the highest temperature of the suspension was 37°C, and it did not exceed 50°C. In this way, a slurry containing the primary ACP particle having the particle diameter less than about 0.1 μm was obtained.

[0015] A HAp spherical particle was manufactured using the slurry by a spray drying granulation method. A diagram of a spray drying granulation apparatus used at this time is shown in Fig. 1. In this Fig.1, the reference numeral 9 denotes an air filter, the reference numeral 10 denotes an electric heater. It was made such that the heated air traveling through the air filter 9, and being heated by the electric heater 10 enters into a spray dryer 5 from a heating gas chamber 11, while a slurry 3 sprayed by an atomizer 6 of

the spray drier 5 is dried and granulized by the heated air, and the relevant heated air is flown out toward a cyclone 8 from the discharge orifice 12.

[0016] The slurry 3 containing the obtained primary ACP particle 1 was supplied to the atomizer 6 of the spray drier 5 (ODB - 25G manufactured by Ohkawara Kakohki, Co., Ltd.) by a metering pump 4. The mixed matter, the slurry 3 was sprayed into the heated air flow for drying within the spray drier 5 by high-speed revolution of the atomizer 6, and the granulation was carried out by a spray drying granulation method. An ACP porous spherical particle 7 was obtained by this granulation.

[0017] The obtained ACP porous particle 7 was collected by the cyclone 8. At this time, a super-fine powder body which was not collected by the cyclone 8 was separately collected by a bug filter (not shown). It should be noted that the operating conditions in the granulation were as follows. The supplied amount of the mixed matter by the metering pump 4 was in the range from 1 to 3 kg/h, as for the temperature of the heated air heated by the electric heater 10 via the air filter 9, the temperature was controlled such that the temperature of the inlet of the heating gas chamber 11 was in the range from 150 to 350°C and the temperature of the outlet of the discharge orifice 12 communicating to the cyclone 8 always exceeded 80°C, and it was set so that the number of revolutions of the atomizer 6 was in the range from 10000 to 30000 rpm.

[0018] The ACP porous particle 7 thus obtained was a porous spherical shape by utilizing a spray drying granulation method, and the average particle diameter was 35 μm. The ACP particle was put in an alumina skull crucible furnace, burned at 1200°C for one hour, and a HAp spherical particle was obtained. 1 g of this HAp spherical particle was taken and put in 25 g of ion-exchanged water, filtered after it was agitated for 10 minutes by a stirrer, and when pH of the filtered liquid was measured, the pH value of it was 9.6.

[0019] Comparative Example 1

After 10% calcium hydroxide suspension was cooled to about 10°C while agitating it, 0.5% by weight of weak alkaline ammonium triacrylate as an aqueous dispersing agent

was added, and the mixture solution was obtained. While the mixture solution was agitated, phosphoric acid aqueous solution in which 85% phosphoric acid aqueous solution had been diluted with water into 10-fold was dropped, and then, an ACP slurry was synthesized by adjusting pH into 10.5. In the synthesis reaction, the highest temperature of the suspension was 37°C, and it did not exceed 50°C. In this way, a slurry containing the primary ACP particle having the particle diameter less than about 0.1 μm was obtained. 1 g of the HAp particle obtained by performing the drying granulation and burning under the conditions similar to those of Example 1 was taken, put in 25 g of ion-exchanged water, filtered after it was agitated by a stirrer, and when pH of the filtered liquid was measured, the pH value of it was 7.5.

[0020] Test Example 1

(Animal Test)

Material

The HAp spherical particle prepared in Example 1 and the HAp particle prepared in Comparative Example 1 were used. Moreover, Sprague-Dawley rat (7 weeks age, male) was used as an experimental animal.

[0021] Experimental Method

Using a round bur for dentistry, on the skull of a rat to which the general anesthesia was carried out, the fracture part having the diameter of about 2.5 mm was prepared. The macroscopically sufficient amount of the HAp was filled in this fracture part, respectively. After filling it, the skull was collected after two and four weeks, it was fixed by 10% neutral formalin solution. At the time of histopathological observation, after the decalcification of the skull was performed by 10% EDTA solution, HAp refilled part was cut out, alcohol dehydration and xylene penetration were performed, and were embedded in paraffin. Subsequently, the tissue sample of about 4 μm was prepared and hematoxylin/eosin staining was performed to it and the observation by a light microscopy and the shooting were performed.

[0022] Results

A microscopic photograph taken after two weeks, in which a HAp spherical particle of Example 1 was refilled, is shown in Fig. 2, and a microscopic photograph taken after two weeks, in which a HAp of Comparative Example 1 was filled is shown in Fig. 3. In these microscopic photographs, the reference character B denotes a skull (existing bone), and the arrow indicates the fractured end of the fractured part. In both of HAp particle refilling examples, the bone conduction findings were observed; however, in the case of the HAp refilling agent of Example 1, a newly formed bone tissue was observed within the fractured part. From this fact, it is indicated that the HAp particle of Example 1 provides more appropriate environment comparing to the HAp particle of Comparative Example 1.

[0023] A microscopic photograph taken after four weeks, in which a HAp spherical particle of Example 1 was refilled, is shown in Fig. 4, and a microscopic photograph taken after four weeks, in which a HAp of Comparative Example 1 was filled is shown in Fig. 5. In these microscopic photographs, the reference character B denotes a skull (existing bone), the reference character b denotes a newly formed bone, the reference character c denotes a connective tissue, the reference character H denotes a HAp particle, and the arrow indicates the fractured end of the fractured part. As shown in Fig. 4, a large number of HAp particle have been charged within the newly formed bone in the HAp particle refilled example of Example 1. In contrast to this, in the HAp particle refilled example of Comparative Example 1, the new formation degree of the bone is bad, and the HAp particle remained surrounded by the connective tissue. Moreover, in the microscopic photograph of the HAp particle refilled example of Example 1 (Fig. 4), a large number of scars in a seamed shape are admitted. These were made at the time when the histopathological sample was prepared since the newly formed bone tissue was too hard although the decalcification treatment was performed, and it indicates that the newly formed bone is extremely strong.

[0024]

[Effect of the Invention] A hydroxyapatite of the present invention is excellent in bone formation capability, and it can be preferably used for a bone refilling material, a filling material for refilling within a tooth root canal, a filling material for tooth extraction cavity and a material for reconstructing alveolar ridge.

[Brief Description of the Drawings]

[Fig. 1] Fig. 1 is a drawing showing a granulation drying apparatus used for the preparation of an amorphous calcium phosphate particle of the present invention.

[Fig. 2] Fig. 2 is a photograph showing a microscopic image taken two weeks after the HAp spherical particle obtained in Example 1 was refilled in the fractured part of the skull of a rat.

[Fig. 3] Fig. 3 is a photograph showing a microscopic image taken two weeks after the HAp particle obtained in Comparative Example 1 was refilled in the fractured part of the skull of a rat.

[fig. 4] Fig. 4 is a photograph showing a microscopic image taken four weeks after the HAp spherical particle obtained in Example 1 was refilled in the fractured part of the skull of a rat.

[Fig. 5] Fig. 5 is a photograph showing a microscopic image taken two weeks after the HAp particle obtained in Comparative Example 1 was refilled in the fractured part of the skull of a rat.

[Description of the reference numerals and characters]

1: primary ACP particle

3: slurry containing a primary ACP particle

4: metering pump

5: spray drier

6: atomizer

7: ACP porous particle

8: cyclone

9: air filter

10: electric heater

11: heating gas chamber

12: discharge orifice

B: skull (originally existing bone)

b: newly formed bone (newly formed bone)

c: connective tissue

H: apatite particle

Fig.1

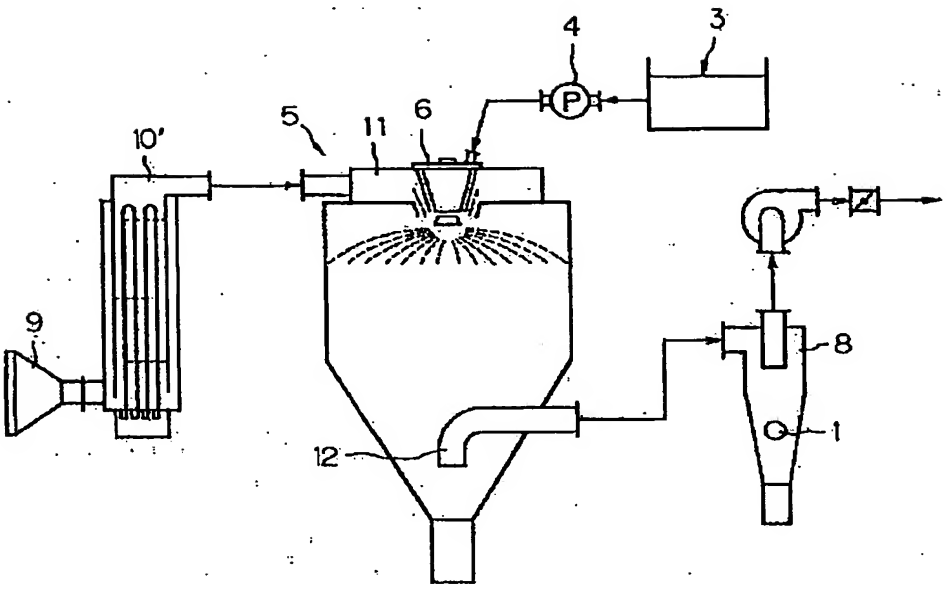

Fig.2

Picture as substitute for diagram

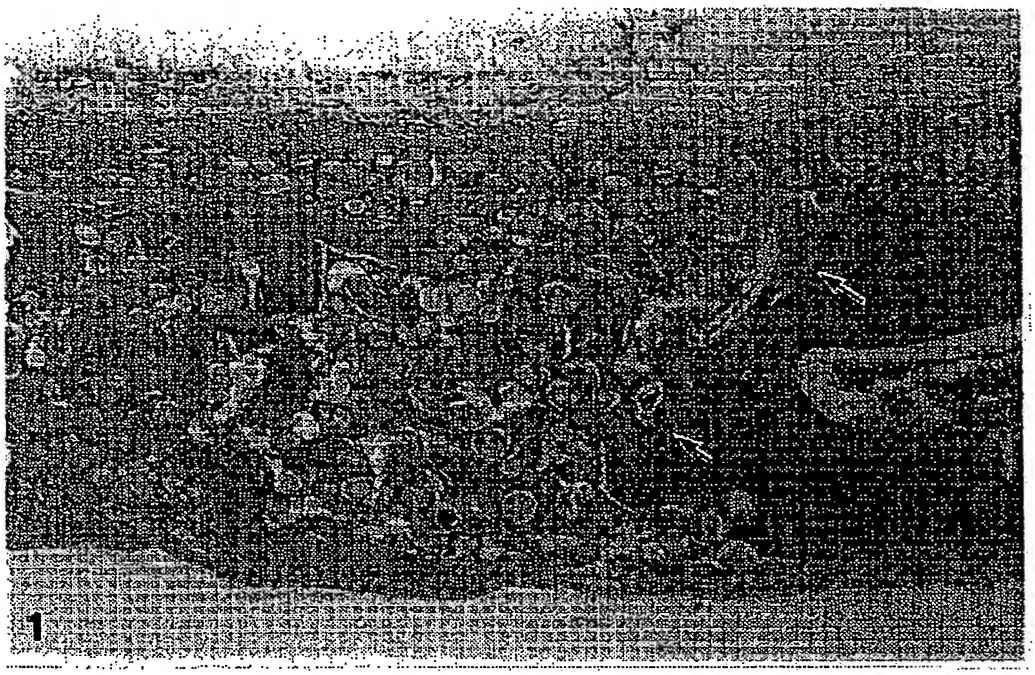

Fig.3

Picture as substitute for diagram

Fig.4

Picture as substitute for diagram

Fig.5

Picture as substitute for diagram